How can drugs induce **Thrombocytopenia?**

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Objectives

Review bibliographical data on **Drug-Induced Thrombocytopenia (DITP)**, a potentially serious adverse event caused by some medications. The main aim is to elucidate what is DITP, its causing mechanims, its diagnostic criteria and the prevalence of DITP since 2010.

Methods

Compiled data have been reviewed from databases such as **Pubmed**, **Medline** and **ScienceDirect** using the keywords *'Thrombocytopenia/DITP'*. The results of the search were further matched with information provided from the University of Oklahoma website focused on platelet disorders[4].

Background

Platelets are anucleated cells produced in the bone marrow from megakaryocytes, circulate 7-10 days in peripheral blood (150.000–450.000/μL) and then are destroyed in the spleen and liver. They play a very important role in haemostasis making blood clot and help stop bleeding.

Platelets contain several types of **glycoproteins** in their membrane expressing a set of antigens (Figure 2). These antigens can be recognized by auto-antibodies or alloantibodies, increasing platelet destruction.

Thrombocytopenia is a persistent decrease in the number of blood platelets <100.000/μL.

According to its pathophysiology, thrombocytopenia can be classified as caused by:

- a decrease in the platelet production
- an increase in the destruction of platelets
- sequestration in the spleen
- Haemodilution

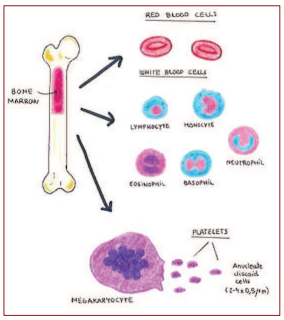


Figure 1: Haematopoiesis in bone marrow.

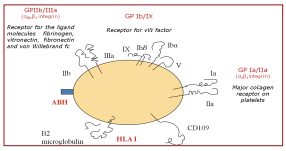


Figure 2:Main GPs complexes present on the platelet surface[1].

If it becomes sever, cutaneous bleeding, epistaxis, gingival bleeding, hematuria, or other hemorrhagic complications can occur

DITP can be caused by several immune or non-immune mechanisms

- **Non-immune DITP**: megakaryocyte proliferation impairment
- **Immune-mediated DITP** platelet destruction due to drug-dependent platelet-antibodies. It can be caused by certain foods and beverages

Mechanisms proposed to explain immune-mediated DITP:

a) Mechanism of Adsorption

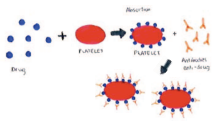


Figure 3: Mechanism of adsorption. The drug is adsorbed, binds to platelet GPs and drug-dependent antibodies react with cells[2].

b) Mechanism of immune-complexes

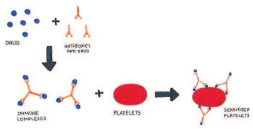


Figure 4: Mechanism of immune-complexes. The drug induces the synthesis of antibodies specific for them and then both antibody and drug can be joined to form an immune complex capable of reacting with platelets[2].

c) Mechanism of haptens

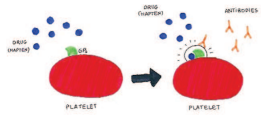


Figure 5: Mechanism of hapten-induced antibodies. Drug molecules are too small to be immunogenic, but when they bind to platelets, they formed a hapten-platelet complex that induces the production of specific hapten antibodies[2].

d) Mechanism of fibans

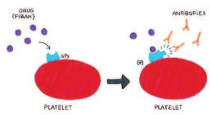


Figure 6: Mechanism of fibans. Fibans bind platelet GPs and change their conformation, inducing the emergence of neoepitopes, which become the target of antibodies[2].

e) Mechanism of autoantibody formation

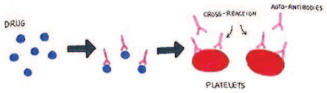


Figure 6: Mechanism of auto-antibodies formation. The drug induce the formation of drug-independent platelet autoantibodies that bind to platelet antigens even in the absence of the drug. The resultant thrombocytopenia can persist after the drug is discontinued[2].

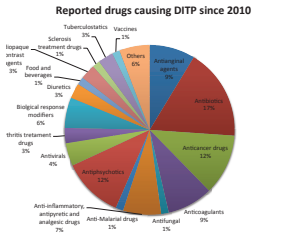
In some cases, DITP can be mistaken for other immune reactions such as ITP. Immune Thrombocytopenic Purpura (ITP) is due to the presence of autoantibodies against platelet GPs. Moreover, platelet GPs have polymorphisms that can induce alloantibody appearance after pregnancy or platelet transfusions.

So, DITP laboratory tests result comparable to these immune reactions that cause thrombocytopenia because they only demonstrate the presence of antibodies against platelets, but not their cause.

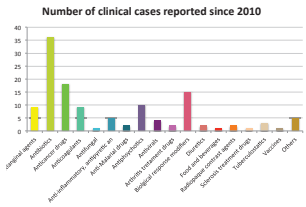
Prevalence research

- 126 clinical cases concerning 69 different drugs or chemicals causing DITP, including food and beverages, have been reported since 2010.
- Results are summarized in the next table and figures:

Drug category	Examples
Antianginal agents	Amiodarone, Amlodipine, Carvedilol, Clopidogrel, Furosemide and Iloprost
Antibiotics	Amoxicillin, Cefazolin, Ceftriaxone, Levofloxacin, Linezolid, Moxifloxacin, Nitrofurantoin, Piperacillin, Rifabutin, Rifampicin, Trimetoprim, Vancomycin
Anticancer drugs	Adalimumab, Alfuzosin, Bortezomib, Dorzolamide, Filgrastim, Ipilimumab, Oxiplatin and Temozolomide
Anticoagulants	Abciximab, Dipyriamole, Eptifibatide, Protamine sulfate, Rivaroxaban and Tirofiban
Antifungal	Fluconazol
Anti-inflammatory drugs	Diclofenac, Meloxicam, Metamizol, Salicilate and Aspirin
Anti-malarial drugs (Cinchona alkaloid)	Quinine
Antipsychotic drugs	Carbamazepine, Lamotrigine, Levetiracetam, Olanzapine, Oxcarbazepine, Phenobarbital, Phenytoin and Quetiapine
Antiviral drugs	Peramivir, INF-α and Cinobufacini
Arthritis treatment drugs	Hydroxychloroquine and Methylprednisolone
Biological response modifiers	Etanercept, Infliximab, Rituximab and Trastuzumab
Diuretics	Rosuvastatin and Simvastatin
Food and beverages	Nutshell
Radiopaque contrast agents	Iopamidol and Ioversol
Sclerosis treatment drugs	Natalizumab
Tuberculostatics	Isoniazid and Pyrazinamide
Vaccines	Measles- Rubella Vaccine
Others	Repaglinide (antidiabètic drug) Pantoprazole (treatment gastroesophageal reflux disease) Galsulfase (Enzyme replacement therapy) Pirazetam (noontropic drug)



gure 8: Graphic data of the % of reported drugs causing DITP nce 2010[4].



gure 9: Histogram showing the number of cases ported for every drug found in the search since 2010[4].

Diagnostic criteria

- A systematic clinical history is essential in establishing the diagnosis of DITP, (exposure to drugs, herbal preparations, certain foods and beverages)
- Differential diagnosis with ITP is important for the patient's treatment
- Clinical criteria have been established to determine the likelihood of a drug being the cause DITP (definite, probable, possible and unlikely according to the criteria stipulated)
- Laboratory Tests: drug-dependent platelet-antibodies can be detected in the patient serum, by different in vitro techniques using flow cytometry.

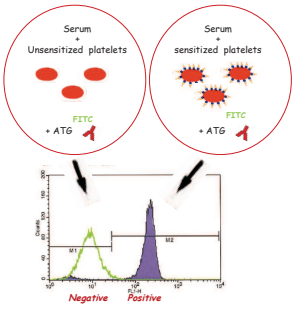


Figura 10: Positive and negative results from a cytometry flow laboratory test to demonstrate the presence of antibodies in the serum of patients with DITP[3].

Conclusions

- It is difficult to know the real incidence of DITP
- Limited number of published reports of DITP for the last five years
- There is a need to established uniform methods to improve the reproducibility of results to enable reliable comparisons.
- There is a need to report new cases in a single central database useful as a global reference for the correct diagnostic and the most suitable treatment of DITP.

References:
[1] Image courtesy of Dr. Carme Canals (Laboratory of Immunohaematology of the Blood and Tissue Bank in Barcelona.
[2] Arnold, Donald M., et al. "Approach to the diagnosis and management of drug-induced immune thrombocytopenia." *Transfusion medicine reviews* 27.3 (2013): 137-145.
[3] Image courtesy of Dr. Carme Canals (Laboratory of Immunohaematology of the Blood and Tissue Bank in Barcelona.
[4] *Platelets on the Web* [online]. University of Oklahoma Health Sciences Center: James N. George, 2007[consulted: April 2015]. Available: http://www.ouhsc.edu/platelets/